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Dated 4 August 2003

Patents Form 1/77

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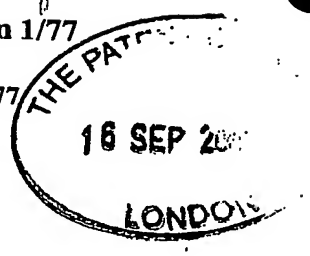

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PCT/EP 03/11065

1/77

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17SEP02 E748612-1 D02029
P01/7700 0.00-0221443.5

1. Your reference — ACC/DAB/PG4893

2. Patent application number
(The Patent Office will fill in his part) — 0221443.5 — 16 SEP 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

8202930 01

United Kingdom

4. Title of the invention — PYRIDINE DERIVATES

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)*

Corporate Intellectual Property

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980 Great West Road
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Middlesex TW8 9GS

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6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
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Request for preliminary examination and search *(Patents Form 9/77)*	
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11. We request the grant of a patent on the basis of this application
Signature ACConnell. Date 12-Sep-02
A C Connell

12. Name and daytime telephone number of person to contact in the United Kingdom — A C Connell 01279 644395

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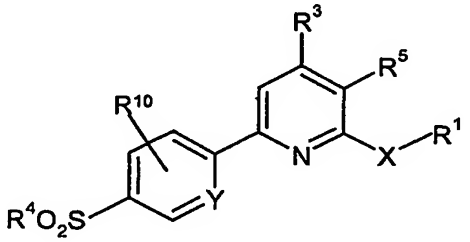
PYRIDINE DERIVATIVES

This invention relates to pyridine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

The enzyme cyclooxygenase (COX) has recently been discovered to exist in two isoforms, COX-1 and COX-2. COX-1 corresponds to the originally identified constitutive enzyme while COX-2 is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. Prostaglandins generated by the action of COX have both physiological and pathological roles. It is generally believed that COX-1 is largely responsible for the important physiological functions such as maintenance of gastrointestinal integrity and renal blood flow. In contrast the inducible form, COX-2, is believed to be largely responsible for the pathological effects of prostaglandins where rapid induction of the enzyme occurs in response to such agents as inflammatory agents, hormones, growth factors and cytokines. A selective inhibitor of COX-2 would therefore have anti-inflammatory, anti-pyretic and analgesic properties, without the potential side effects associated with inhibition of COX-1. We have now found a novel group of compounds which are both potent and selective inhibitors of COX-2.

The invention thus provides a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof in which:

X is selected from the group consisting of oxygen or NR^2;
Y is selected from the group consisting of CH or nitrogen;
R^1 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-2}alkyl substituted by one to five fluorine atoms, C_{1-3}alkylOC_{1-3}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-} ...cycloalkylC_{0-6}alkyl, C_{4-12}bridged cycloalkyl, $A(CR^6R^7)_n$ and $B(CR^6R^7)_n$;
R^2 is selected from the group consisting of H and C_{1-6}alkyl; or

R^1 and R^2, together with the nitrogen atom to which they are attached form a 4-8 membered saturated heterocyclic ring such as a pyrrolidine, morpholine or piperidine ring;

R^3 is selected from the group consisting of C_{1-5}alkyl and C_{1-2}alkyl substituted by one to five fluorine atoms;

R^4 is selected from the group consisting of C_{1-6}alkyl, NH_2 and R^9CONH;

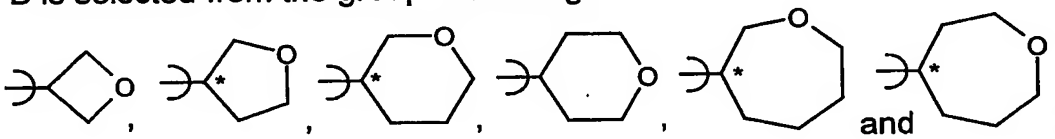
R^5 is selected from the group consisting of hydrogen, C_{1-3}alkyl, C_{1-2}alkyl substituted by one to five fluorine atoms, halogen, cyano, $(C_{1-3}alkyl)_2NCO$, $C_{1-3}alkylS$ and $C_{1-3}alkylO_2S$;

R^6 and R^7 are independently selected from H or C_{1-6}alkyl;

A is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R^8;

R^8 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one more fluorine atoms, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more F, NH_2SO_2 and $C_{1-6}alkylSO_2$;

B is selected from the group consisting of



and where

) defines the point of attachment of the ring;

R^9 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}alkoxy, $C_{1-6}alkylOC_{1-6}$alkyl, phenyl, HO_2CC_{1-6}alkyl, $C_{1-6}alkylOCOC_{1-6}$alkyl, $C_{1-6}alkylOCO$, H_2NC_{1-6}alkyl, $C_{1-6}alkylOCONHC_{1-6}$alkyl and $C_{1-6}alkylCONHC_{1-6}$alkyl;

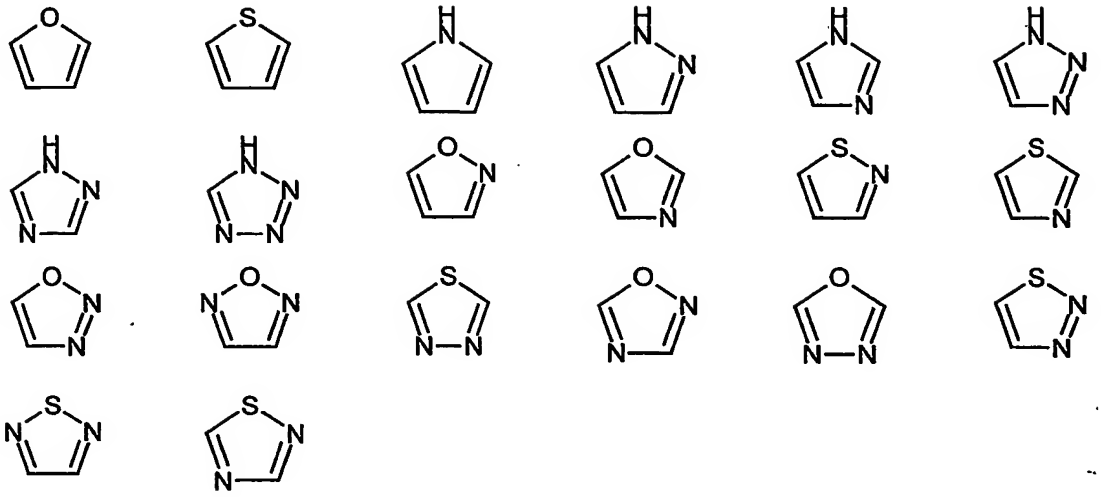
R^{10} is selected from the group consisting of H and halogen; and

n is 0 to 4.

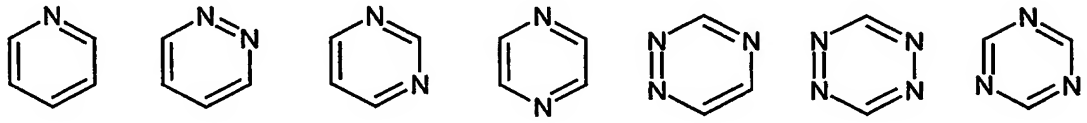
The term halogen is used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

The term 5-membered heteroaryl means a heteroaryl selected from the following:



The term 6- membered heteroaryl means a heteroaryl selected from the following:



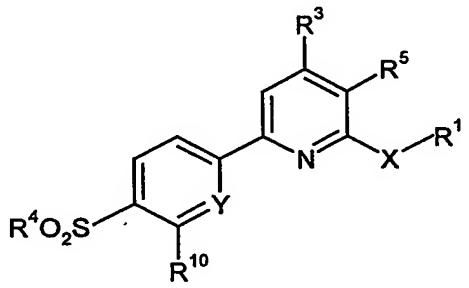
The term 6-membered aryl means:

It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). In particular when the ring B lacks a plane of symmetry the compounds of formula (I) contain a chiral centre as indicated therein by the asterisk *. Furthermore, it will be appreciated by those skilled in the art that when R^6 and R^7 in formula (I) are different the corresponding compounds contain at least one chiral centre, by virtue of the asymmetric carbon atom defined thereby, and that such compounds exist in the form of a pair of optical isomers (i.e. enantiomers).

It will be appreciated that in some instances, compounds of the present invention may include a basic function such as an amino group as a substituent. Such basic functions may be used to form acid addition salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Such salts may be formed from inorganic and organic acids. Representative examples thereof include maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, taurocholic acid, benzenesulfonic, p-toluenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

It will be appreciated that in some instances, compounds of the present invention may include a carboxy group as a substituent. Such carboxy groups may be used to form salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, **66**, 1-19. Preferred salts include alkali metal salts such as the sodium and potassium salts.

In one aspect the invention provides a compound of formula (IA)



(IA)

or a pharmaceutically acceptable salt thereof, in which all substituents are as for a compound of formula (I) defined hereinabove.

In another aspect of the invention Y is carbon.

In another aspect of the invention R^1 is selected from the group consisting of, C_{1-6}alkyl, C_{3-10}cycloalkylC_{0-6}alkyl, C_{1-3}alkylOC_{1-3}alkyl and C_{1-2}alkyl substituted by one to five fluorine atoms.

Representative examples of R^1 include cyclohexylmethyl, cyclohexyl, n-butyl, n-pentyl, cyclopentyl, 2-methylpropyl, 2,2-dimethylpropyl, 2,2,2-trifluoroethyl, 2-methoxyethyl and ethyl.

In another aspect of the invention R^1 is selected from the group consisting of $A(CR^6R^7)_n$ and $B(CR^6R^7)_n$.

Further representative examples of R^1 include benzyl, 4-chlorobenzyl, 2-furylmethyl, 4-methylphenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-pyridyl, 2-chlorophenyl, 3,5-difluorobenzyl, 3-pyridylmethyl, 2-methylbenzyl, 2-chlorobenzyl, (*S*)-α-methylbenzyl, (*R*)-α-methylbenzyl, 6-methylpyridin-3-yl, 4-methoxybenzyl, 4-fluorobenzyl, 2-(5-methylfuryl)methyl, 4-methylbenzyl, 4-pyridylmethyl, 2-pyridylmethyl, 2-(6-methylpyridine)methyl, 2-thiophenylmethyl, 4-pyranylmethyl, 2-tetrahydrofurylmethyl, 2-(5-methylpyrazine)methyl and 4-ethoxybenzyl.

In another aspect of the invention R^1 is selected from the group consisting of C_{3-6}alkenyl and C_{3-6}alkynyl.

Further representative examples of R^1 include propargyl and allyl.

In another aspect of the invention R^2 is H or C_{1-2}alkyl.

In another aspect of the invention R^3 is CHF_2, CH_2F, CF_3 or C_{1-4}alkyl.

Representative examples of R^3 include CF_3, CH_3 and ethyl.

In another aspect of the invention R^4 is C_{1-6}alkyl, such as C_{1-3}alkyl.

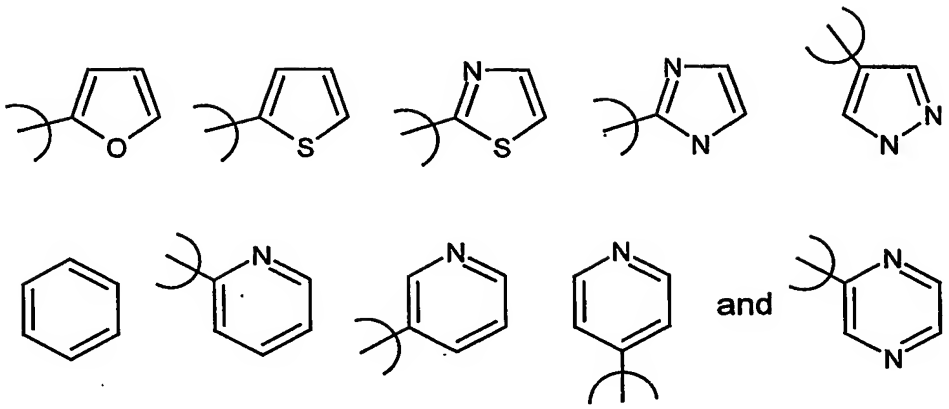
Representative examples of R^4 include CH_3.

In another aspect of the invention R^5 is hydrogen or C_{1-3}alkyl.

Representative examples of R^5 include H or CH_3.

In another aspect of the invention R^6 and R^7 are independently selected from H or methyl. In another aspect R^6 and R^7 are both H.

In another aspect of the invention A is selected from the group consisting of



where) defines the point of attachment of the ring
and A is unsubstituted or substituted by one or two R^8.

In another aspect of the invention R^8 is selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkyl substituted by one to three fluorine atoms (e.g. CF_3), and C_{1-3}alkoxy.

Representative examples of R^8 include F, Cl, CH_3, methoxy and ethoxy.

In another aspect of the invention R^9 is selected from the group consisting of C_{1-6}alkyl (e.g. ethyl), phenyl and aminomethyl.

In another aspect of the invention R^{10} is H.

In another aspect of the invention n is 0 to 2 (e.g. 1).

It is to be understood that the invention covers all combinations of particular aspects of the invention as described hereinabove.

Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compound of formula (I) may be used for preparing the more pure forms used in pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever

possible, the compounds of the present invention are available in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are recrysallised from organic solvents, solvent of recrystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all the polymorphic forms of the compounds of formula (I).

Compounds of the invention are potent and selective inhibitors of COX-2. This activity is illustrated by their ability to selectively inhibit COX-2 over COX-1.

In view of their selective COX-2 inhibitory activity, the compounds of the present invention are of interest for use in human and veterinary medicine, particularly in the treatment of the pain (both chronic and acute), fever and inflammation of a variety of conditions and diseases mediated by selective inhibition of COX-2. Such conditions and diseases are well known in the art and include rheumatic fever; symptoms associated with influenza or other viral infections, such as the common cold; lower back and neck pain; headache; toothache; sprains and strains; myositis; sympathetically maintained pain; synovitis; arthritis, including rheumatoid arthritis; degenerative joint diseases, including osteoarthritis; gout and ankylosing spondylitis; tendinitis; bursitis; skin related conditions, such as psoriasis, eczema, burns and dermatitis; injuries, such as sports injuries and those arising from surgical and dental procedures.

The compounds of the invention are also useful for the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific

lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of the invention are also useful for the treatment of other conditions mediated by selective inhibition of COX-2.

For example, the compounds of the invention inhibit cellular and neoplastic transformation and metastatic tumour growth and hence are useful in the treatment of certain cancerous diseases, such as colonic cancer and prostate cancer. The compounds of the invention are also useful in reducing the number of adenomatous colorectal polyps and thus reduce the risk of developing colon cancer. The compounds of the invention are also useful in the treatment of cancer associated with overexpression of HER-2/neu, in particular breast cancer.

Compounds of the invention also prevent neuronal injury by inhibiting the generation of neuronal free radicals (and hence oxidative stress) and therefore are of use in the treatment of stroke; epilepsy; and epileptic seizures (including grand mal, petit mal, myoclonic epilepsy and partial seizures).

Compounds of the invention also inhibit prostanoid-induced smooth muscle contraction and hence are of use in the treatment of dysmenorrhoea and premature labour.

Compounds of the invention are also useful in the treatment of liver disease, such as inflammatory liver disease, for example chronic viral hepatitis B, chronic

viral hepatitis C, alcoholic liver injury, primary biliary cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis and liver transplant rejection.

Compounds of the invention inhibit inflammatory processes and therefore are of use in the treatment of asthma, allergic rhinitis and respiratory distress syndrome; gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis; and the inflammation in such diseases as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, type I diabetes, myasthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, conjunctivitis and myocardial ischemia.

Compounds of the invention are also useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis and of acute injury to the eye tissue.

Compounds of the invention are also useful for the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease), and vascular dementia (including multi-infarct dementia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

Compounds of the invention are also useful in the treatment of disorders ameliorated by a gastroprokinetic agent. Disorders ameliorated by gastroprokinetic agents include ileus, for example post-operative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); gastroparesis, such as diabetic gastroparesis; and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP).

According to a further aspect of the invention, we provide a compound of formula (I) for use in human or veterinary medicine.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by COX-2 which comprises administering to said subject an effective amount of a compound of formula (I).

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from an inflammatory disorder, which method comprises administering to said subject an effective amount of a compound of formula (I).

According to another aspect of the invention, we provide the use of a compound of formula (I) for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by COX-2.

According to another aspect of the invention, we provide the use of a compound of formula (I) for the manufacture of a therapeutic agent for the treatment of an inflammatory disorder.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more other therapeutic agents. Examples of suitable agents for adjunctive therapy include a $5HT_1$ agonist, such as a triptan (e.g. sumatriptan or naratriptan); an adenosine A1 agonist; an EP ligand; an NMDA modulator, such as a glycine antagonist; a sodium channel blocker (e.g. lamotrigine); a substance P antagonist (e.g. an NK_1 antagonist); a cannabinoid; acetaminophen or phenacetin; a 5-lipoxygenase inhibitor; a leukotriene receptor antagonist; a DMARD (e.g. methotrexate); gabapentin and related compounds; a tricyclic antidepressant (e.g. amitryptilline); a neurone stabilising antiepileptic drug; a mono-aminergic uptake inhibitor (e.g. venlafaxine); a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS) inhibitor, such as an iNOS or an nNOS inhibitor; an inhibitor of the release, or action, of tumour necrosis factor α; an antibody therapy, such as a monoclonal antibody therapy; an antiviral agent, such as a nucleoside inhibitor (e.g. lamivudine) or an immune system modulator (e.g. interferon); an opioid analgesic; a local anaesthetic; a stimulant, including caffeine; an H_2-antagonist (e.g. ranitidine); a proton pump

inhibitor (e.g. omeprazole); an antacid (e.g. aluminium or magnesium hydroxide; an antiflatulent (e.g. simethicone); a decongestant (e.g. phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine); an antitussive (e.g. codeine, hydrocodone, carmiphen, carbetapentane, or dextramethorphan); a diuretic; or a sedating or non-sedating antihistamine. It is to be understood that the present invention covers the use of a compound of formula (I) in combination with one or more other therapeutic agents.

The compounds of formula (I) are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) adapted for use in human or veterinary medicine. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

As will be appreciated by the person skilled in the art the compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. In particular, for those compounds which demonstrate poor bioavailability, finely divided (nanoparticulate) preparations of the compounds of the invention may be prepared by processes known in the art, for example see International Patent Application No. WO 02/00196 (SmithKline Beecham).

The compounds of formula (I) may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I).

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

As stated above, the compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) together with a further therapeutic agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

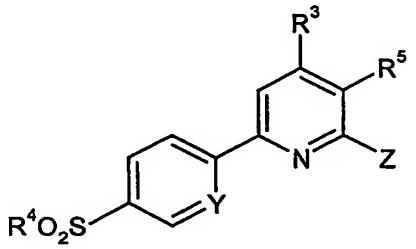
When a compound of formula (I) is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A proposed daily dosage of a compound of formula (I) for the treatment of man is 0.01mg/kg to 500mg/kg, such as 0.05mg/kg to 100mg/kg, e.g. 0.1mg/kg to 50mg/kg, which may be conveniently administered in 1 to 4 doses. The precise dose employed will depend on the age and condition of the patient and on the route of administration. Thus, for example, a daily dose of 0.25mg/kg to 10mg/kg may be suitable for systemic administration.

Compounds of formula (I) may be prepared by any method known in the art for the preparation of compounds of analogous structure.

Compounds of formula (I) may be prepared by a process which comprises:

reacting a compound R^1XH of formula (II), or a protected derivative thereof, with a compound of formula (III)



(III)

where X is as defined and Z is halogen, such as F, Cl, Br or I,or a sulfonate, such as (4-methyl)benzenesulfonate or trifluoromethanesulfonate and thereafter and if necessary,

interconverting a compound of formula (I) into another compound of formula (I); and/or

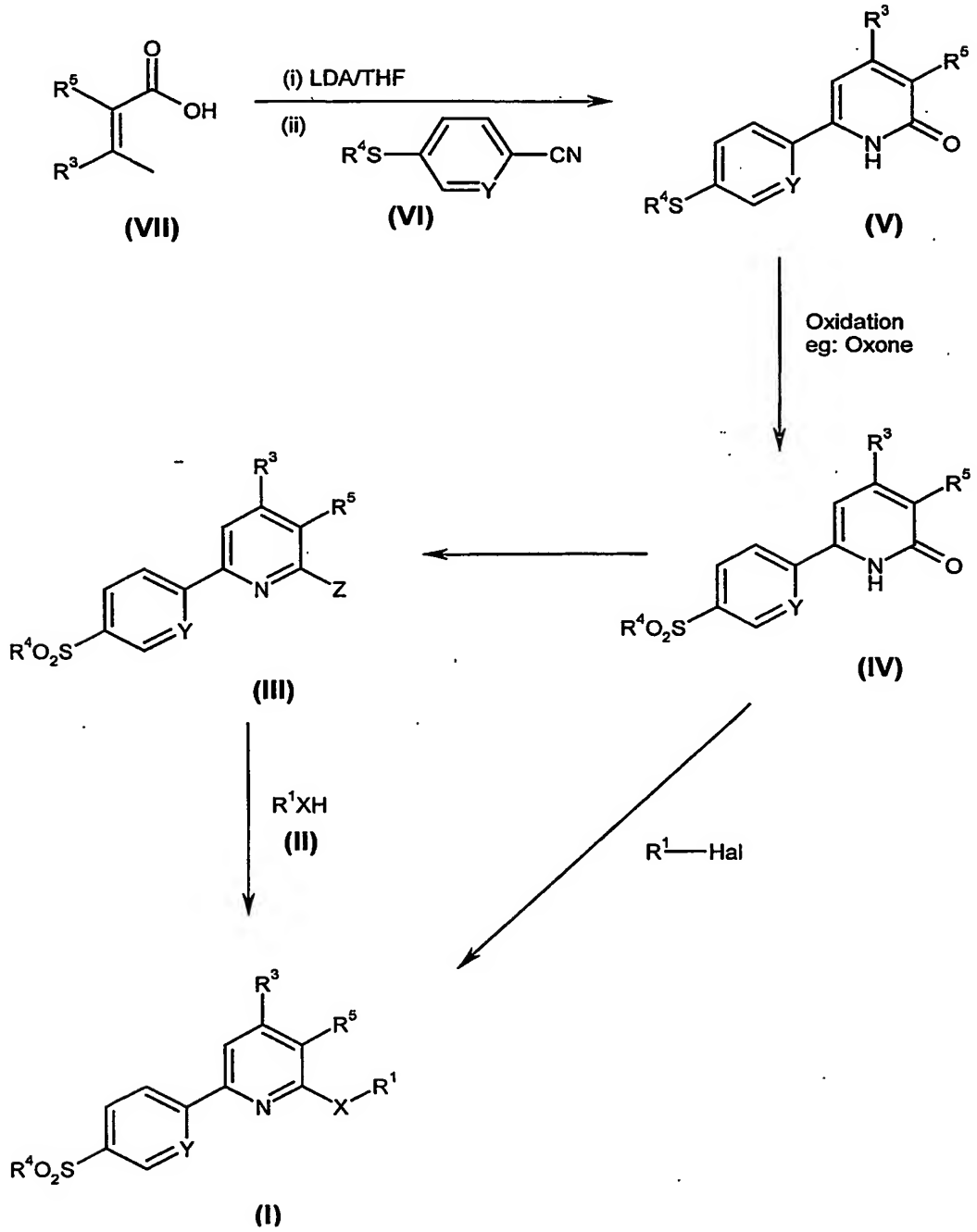
deprotecting a protected derivative of compound of formula (I).

The overall synthesis of a compound of formula (I) is shown in Scheme 1 below in which, R^1 to R^3, R^5, X and Y are as defined in formula (I) unless otherwise stated, R^4 is C_{1-6}alkyl and Z is a halogen, such as F, Cl, Br or I, or a sulfonate, such as (4-methyl)benzenesulfonate or trifluoromethanesulfonate; LDA is lithium diisopropylamide; THF is tetrahydrofuran.

Referring to Scheme 1, when $X=NR^2$, compounds of formula (I) may be prepared via the treatment of compounds of formula (III) with an amine of formula (II). This is conveniently carried out in a solvent, such as a nitrile (e.g.

methylnitrile) and at elevated temperature (e.g. from about 50°C to reflux). An excess of the amine may be used in place of the solvent.

Scheme 1



Alternatively, the treatment of compounds of formula (III) with an amine of formula (II) is conveniently carried out in a solvent, such as a tertiary amine (e.g.

NMP, N-methyl pyrrolidinone) and at elevated temperature (e.g. from 120°C to 250°C) and with or without microwave irradiation.

Alternatively, the treatment of compounds of formula (III) with an amine of formula (II) may be carried out in the presence of a catalytic quantity of a palladium salt, such as palladium (II) acetate, a phosphine ligand, such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), and a base, such as cesium carbonate or sodium tert-butoxide. The reaction is conveniently carried out in a solvent such as toluene or 1,4-dioxan and at elevated temperature.

Referring to Scheme 1, when X=O, compounds of formula (I) may be prepared by the treatment of compounds of formula (III) with an alcohol of formula (II) in the presence of a base such as sodium hydride. The reaction is conveniently carried out in a solvent such as THF and at between ambient temperature and reflux.

Alternatively, when X=O, compounds of formula (I) may be prepared by treatment of 2-pyridones of formula (IV) with an alkyl halide in the presence of a base , such as silver carbonate, and in a solvent, such as DMF (N,N-dimethylformamide) or n-pentane.

Referring to Scheme 1, the conversion of 2-pyridones of formula (IV) to the corresponding pyridines of formula (III) where Z is chlorine or bromine, is conveniently carried out employing a phosphorous halide species (e.g. phosphorous (V) chloride) in a solvent, such as a phosphorous oxyhalide (e.g. phosphorous oxychloride), and at between ambient and elevated temperature (e.g. elevated temperature). Compounds of formula (III) where Z is chlorine or bromine may be converted to compounds of formula (III) where Z is fluorine or iodine using standard interconversion techniques such as those described in 'Comprehensive Organic Transformations: a guide to functional group preparations' by Richard Larock (VCH, 1989), incorporated herein by reference.

Alternatively, the conversion of 2-pyridones of formula (IV) to the corresponding pyridines of formula (III) where Z is a sulfonate, is conveniently carried out in a solvent, such as a nitrogen-containing solvent (e.g. pyridine) and employing a reagent such as a sulfonyl halide (e.g. (4-methyl)benzenesulfonyl chloride) or a sulfonic anhydride (e.g. trifluoromethanesulfonic anhydride).

Conveniently the oxidation shown in Scheme 1 is carried out using a monopersulfate compound, such as potassium peroxymonopersulfate (known as Oxone™) and the reaction is carried out in a solvent, such as an aqueous alcohol (e.g. aqueous methanol) and at between –78°C and ambient temperature.

Alternatively, the oxidation shown in Scheme 1 may be effected using hydrogen peroxide in the presence of sodium tungstate dihydrate. The reaction may be carried out in a solvent such as acetic acid and at between ambient temperature and reflux (e.g. 50°C).

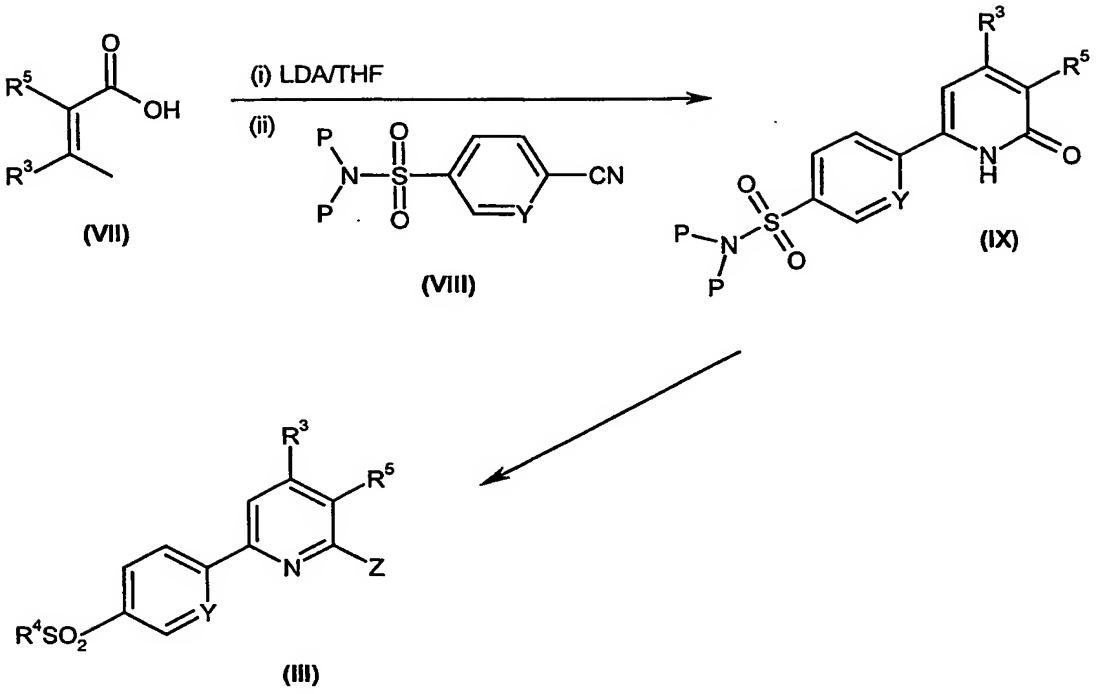
Referring to Scheme 1, pyridones of formula (V) are conveniently prepared by treating α,β-unsaturated acids of formula (VII) with two equivalents of LDA in THF at -78°C, followed by a nitrile of formula (VI), according to the procedure described by E. M. Brown, S. Gil, R. Mestres and M. Pavra in *Synthesis*, 2000, 2, pp 273-280, incorporated herein by reference.

The synthesis of an intermediate of formula (III) in which R^3, R^5 and Y are as defined for compounds of formula (I), Z is a halogen, such as F, Cl, Br or I, or a sulfonate such as (4-methyl)benzenesulfonate or trifluoromethanesulfonate, and R^4 is NH_2, is shown in Scheme 2 below. P represents a suitable protecting group.

Referring to Scheme 2, compounds of formula (IX) may be prepared from compounds of formula (VII) in an analogous manner to that described in Scheme 1. Protection of the sulfonamide functionality of the benzonitrile (VIII) may be achieved using a silicon protecting group, such as the 2-(trimethylsilyl)-ethoxymethyl (SEM) group which can be introduced under standard conditions.

Referring to Scheme 2, the conversion of 2-pyridones of formula (IX) to the corresponding pyridines of formula (III) where Z is halogen, is conveniently carried out employing a phosphorous halide species (e.g. phosphorous (V) chloride) in a solvent, such as a phosphorous oxyhalide (e.g. phosphorous oxychloride), and at between ambient and elevated temperature (e.g. elevated temperature).

Scheme 2



Alternatively, the conversion of 2-pyridones of formula (IX) to the corresponding pyridines of formula (III) where Z is a sulfonate, is conveniently carried out in a solvent, such as a nitrogen-containing solvent (e.g. pyridine) and employing a reagent such as a sulfonyl halide (e.g. (4-methyl)benzenesulfonyl chloride) or a sulfonic anhydride (e.g. trifluoromethanesulfonic anhydride).

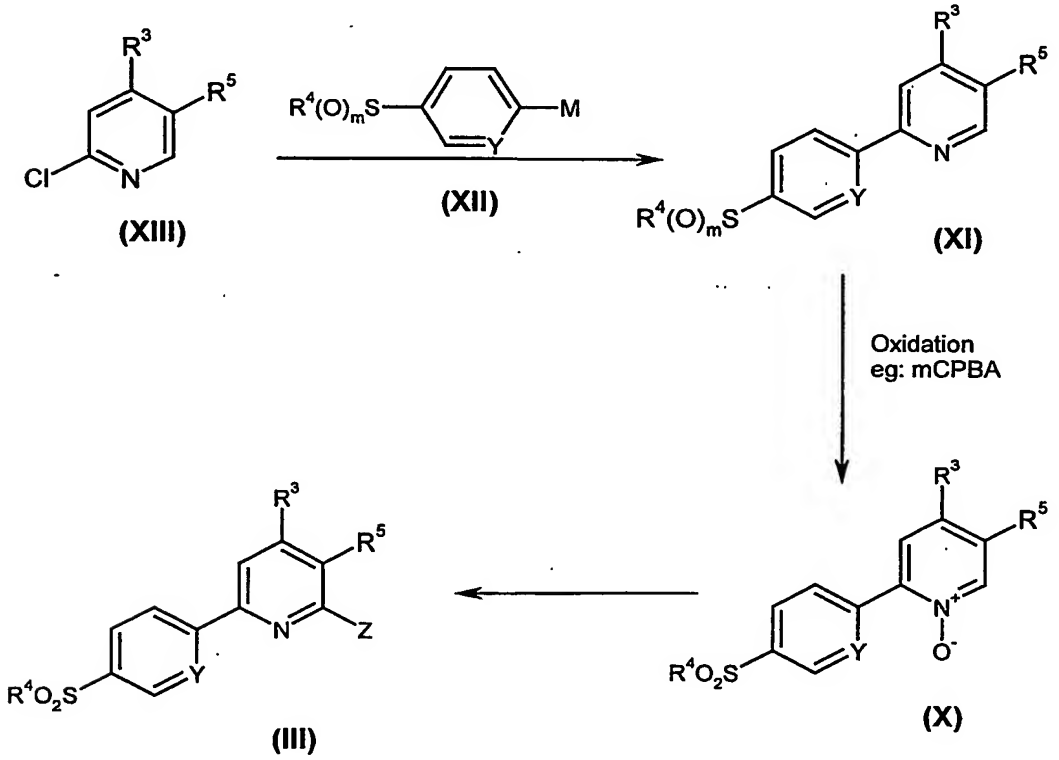
In all alternatives described hereinabove in relation to Scheme 2 for the conversion of (IX) to (III), removal of the protecting groups can be achieved using a source of fluoride, such as tetrabutylammonium fluoride (TBAF), in a suitable organic solvent such as THF, at a temperature between ambient and reflux.

Conversion of the intermediates of formula (III) to compounds of formula (I) can be achieved as described for Scheme 1. In one variation the nitrogen protecting groups on the sulfonamide functionality may be retained during the transformation of intermediates of formula (III) to compounds of formula (I). In some circumstances removal of the protecting groups occurs during the treatment of intermediate (III) with R^1XH (II). Alternatively, the protecting groups

may be removed after treatment of (III) with (II) using the standard deprotection conditions described above.

In one variation of Scheme 1, compounds of formula (III) in which Z is halogen, such as F, Cl, Br and I, may be synthesised according to Scheme 3 below. R^1 to R^3, R^5 and Y are as defined in formula (I) unless otherwise stated, R^4 is C_{1-6}alkyl, M represents $B(OH)_2$ or $B(OR)_2$ and m is 0, 1 or 2.

Scheme 3



Referring to Scheme 3, compounds of formula (XIII) may be converted to compounds of formula (XI) via a Suzuki coupling reaction employing a palladium source, such as palladium tetrakistriphenylphosphine $Pd(PPh_3)_4$, or $Pd_2(dba)_3$ and a ligand, such as triphenylphosphine or tri(tertbutyl)phosphine, and a base, such as sodium carbonate, potassium phosphate or potassium fluoride, in a solvent such as a water/ toluene mix, a water/dimethoxyethane mix or 1,4-dioxan.

Conveniently, the oxidation shown in Scheme 3 is carried out using 3-chloroperoxybenzoic acid (m-CPBA) in a chlorinated solvent, such as

dichloromethane orchloroform, or a mixture of a chlorinated solvent and aqueous sodium bicarbonate ($NaHCO_3$). The oxidation is performed at between 0°C and ambient temperature.

The transformation of (X) to the intermediate (III) may conveniently be achieved via treatment of (X) with a phosphorous halide species (e.g. phosphorous (V) chloride) in a solvent, such as a phosphorous oxyhalide (e.g. phosphorous oxychloride), and at between ambient and elevated temperature (e.g. elevated temperature).

It will be appreciated by those skilled in the art that certain of the procedures described in Schemes 1 to 3 for the preparation of compounds of the formula (I) or intermediates thereto may not be applicable to some of the possible substituents.

It will be further appreciated by those skilled in the art that it may be necessary to carry out the transformations described in Schemes 1 to 3 in a different order from that described, or to modify one or more of the transformations, to provide the desired compound of formula (I).

It will be appreciated by those skilled in the art that compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) as precursors. Suitable interconversions, such as alkylations, are well known to those skilled in the art and are described in many standard organic chemistry texts, such as 'Advanced Organic Chemistry' by Jerry March, fourth edition (Wiley, 1992), incorporated herein by reference. For example, compounds of formula (I) wherein R^1 is $C_{1\text{-}6}$alkyl, $C_{1\text{-}2}$alkyl substituted by one to five fluorine atoms, $C_{3\text{-}6}$alkenyl, $C_{3\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl$C_{0\text{-}6}$alkyl, $C_{4\text{-}12}$bridged cycloalkyl, $A(CR^6R^7)_n$ (with the proviso that n is not zero) or $B(CR^6R^7)_n$ may be prepared by alkylating the corresponding compound of formula (I) wherein R^1 is H.

Acylation of compounds of formula (I) wherein R^4 is NH_2, to provide compounds of formula (I) wherein R^4 is R^9CONH, may be carried out by conventional means, for example by employing conventional acylating agents such as those described in 'Advanced Organic Chemistry', pp 417-424, incorporated herein by reference.

As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the synthesis of compounds of formula (I) to protect one or more sensitive groups in the molecule so as to prevent undesirable side reactions. The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W. Greene and Peter G. M. Wuts, third edition, (Wiley, 1999), incorporated herein by reference, which also describes methods for the removal of such groups.

Amines and alcohols of formula (II) are either known compounds or may be prepared by literature methods, such as those described in 'Comprehensive Organic Transformations: a guide to functional group preparations' by Richard Larock (VCH, 1989), incorporated herein by reference.

Benzonitriles of formula (VI) are either known compounds or may be prepared by literature methods, such as that described by G. Atwell *et al* in *Anti-Cancer Drug Design* **1996**, *11*, 553, incorporated herein by reference.

α,β-Unsaturated acids of formula (VII) are either known compounds or may be prepared by literature methods, such as that described by C. Kuroda *et al* in *Tetrahedron* **2000**, *56*, 6441, incorporated herein by reference.

Certain intermediates described above are novel compounds, and it is to be understood that all novel intermediates herein form further aspects of the present invention. Compounds of formulae (III) and (IV) are key intermediates and represent a particular aspect of the present invention.

Conveniently, compounds of the invention are isolated following work-up in the form of the free base. Pharmaceutically acceptable addition salts of the compounds of the invention may be prepared using conventional means.

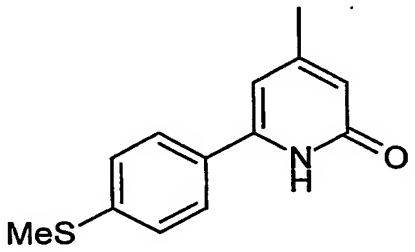
Solvates (e.g. hydrates) of a compound of the invention may be formed during the work-up procedure of one of the aforementioned process steps.

The Intermediates and Examples that follow illustrate the invention but do not limit the invention in any way. All temperatures are in ^{0}C. Silica chromatography refers to either flash column chromatography performed using Biotage column chromatography cartridges or Solid Phase Extraction (SPE) chromatography, using Varian Mega Bond Elut (Si) cartridges (Anachem) under 15mmHg. Thin

layer chromatography (Tlc) was carried out on silica plates. Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 minutes 0%B, 0.7-4.2 minutes linear gradient to 100%B, 4.2-5.3 minutes 0%B, 5.3-5.5 minutes 0%B at a flow rate of 3 ml/minutes. The mass spectra (MS) were recorded on a Waters ZQ mass spectrometer using electrospray positive [(ES+ve to give MH+ and M(NH4)+ molecular ions] or electrospray negative [(ES-ve to give (M-H)-- molecular ion] modes.In addition to those already defined, the following abbreviations are used: Me, methyl; NMP, N- methyl pyrrolidinone; and THF, tetrahydrofuran.

Intermediate 1

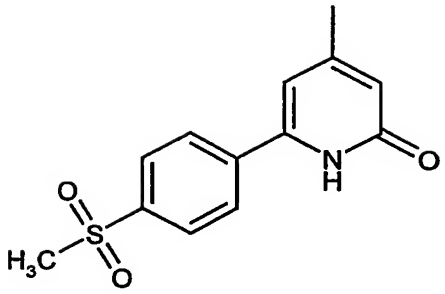
4-Methyl-6-[4-(methylthio)phenyl]-2-pyridone



To a stirred solution of lithium diisopropylamide (50mL of a 2M solution in heptane/THF/ethyl benzene, 0.1mol) in THF (50mL) at –78°C and under an atmosphere of nitrogen was added dropwise a solution of 3-methyl-2-butenoic acid (5g, 0.05mol) in THF (50mL). The reaction was warmed to 0°C for 30 minutes. After cooling to –78°C, a solution of 4-(methylthio)benzonitrile (7.45g, 0.05mol) in THF (50mL) was added dropwise. Upon complete addition, the reaction was warmed to room temperature and stirred for 3 hours. Water (150mL) and ethyl acetate (100mL) were added to the reaction mixture and the resulting precipitate filtered, washed with ethyl acetate and dried to give the title compound (4.96g, 43%) LC retention time 2.75mins, MS m/z 232 (MH^+).

Intermediate 2

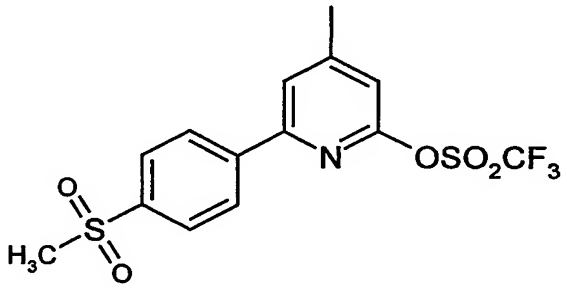
4-Methyl-6-[4-(methylsulfonyl)phenyl]-2-pyridone



To a stirred mixture of intermediate 1 (3.7g, 16.0mmol) in methanol (150mL) at 0°C was added portionwise a suspension of Oxone™ (29.5g, 48.0mmol) in water (100mL). The reaction was warmed to room temperature and stirred for 14 hours. The methanol was removed *in vacuo* and the resulting residue partitioned between saturated aqueous sodium bicarbonate(1L) and chloroform (500mL) and separated. The aqueous layer was further extracted with chloroform (3 x 200mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated to give the title compound (3.20g, 76%) LC retention time 2.20mins, MS m/z 264 (MH^+).

Intermediate 3

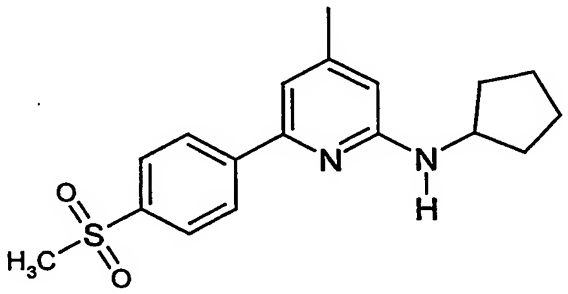
4-Methyl-6-[4-(methylsulfonyl)phenyl]pyridine-2-trifluoromethanesulfonate



To a stirred solution of intermediate 2 (3.20g, 12.2mmol) in pyridine (150mL) at 0°C and under an atmosphere of nitrogen was added dropwise trifluoromethanesulfonic anhydride (2.46mL, 14.6mmol). After stirring for 1hr at 0°C, the pyridine was removed *in vacuo* and the residue partitioned between water (200mL) and dichloromethane (200mL). The layers were separated and the aqueous phase further extracted with dichloromethane (3 x 100mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give the title compound (4.27g, 89%) LC retention time 3.48mins, MS m/z 396 (MH^+).

Example 1

N-Cyclopentyl-4-methyl-6-[4-(methylsulfonyl)phenyl]pyridine-2-amine

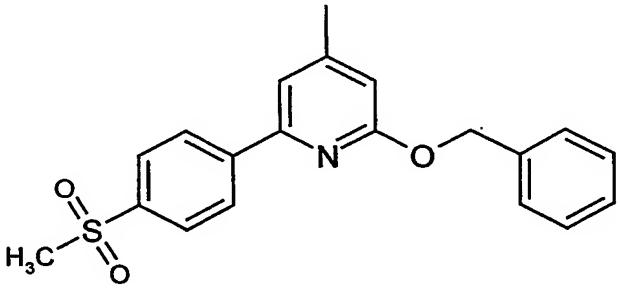


A stirred solution of intermediate 3 (60mg, 0.15mmol) and cyclopentylamine (60µL, 0.76mmol) in NMP (2mL) was heated at 180°C for 14 hours. Removal of the solvent (vacuum centrifuge) and purification by silica chromatography, eluting with a gradient of cyclohexane to ethyl acetate, gave the title compound (17mg, TLC R_F 0.45, 1:1 ethyl acetate:cyclohexane) MS m/z 331 (MH^+).

Example 2

2-Benzyloxy-4-methyl-6-[4-(methylsulfonyl)phenyl]pyridine

Route A



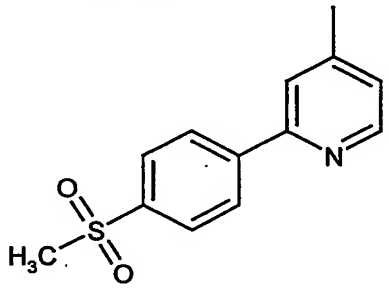
To a stirred solution of intermediate 2 (24mg, 0.09mmol) in DMF (0.5mL) was added silver carbonate (28mg, 0.10mmol) followed by benzyl bromide (13µL, 0.11mmol). The reaction was stirred at room temperature in the dark for 14h hours before being diluted with diethyl ether (5mL), filtered, washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo* to give the title compound (30mg, 93%) LC retention time 3.54mins, MS m/z 354 (MH^+).

Route B

To a stirred suspension of sodium hydride (9mg, 0.22mmol) in DMF (2mL) at room temperature and under an atmosphere of nitrogen was added benzyl alcohol (0.02mL, 0.19mmol). After stirring for 1 hour, the reaction mixture was

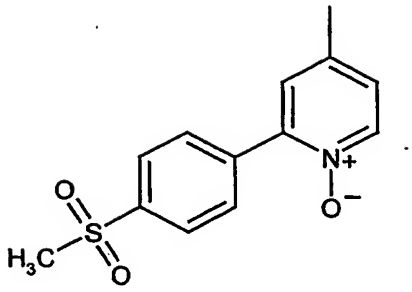
added to intermediate 3 (50mg, 0.13mmol) and the reaction heated at 250°C with microwave irradiation. After cooling, the solvent was removed *in vacuo* and the residue partitioned between water (5mL) and dichloromethane (5mL). The layers were separated and the aqueous phase further extracted with dichloromethane (2 x 5mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated *in vacuo* and purified by silica chromatography eluting with a gradient of ethyl acetate in cyclohexane to give the title compound TLC R_F 0.31 (1:3 ethyl acetate:cyclohexane) LC retention time 3.54mins, MS m/z 354 (MH^+)

Intermediate 4
2-[4-(methylsulfonyl)phenyl]-4-methylpyridine



To a mixture of 2-chloro-4-methylpyridine (3g, 23.5mmol), 4-(methylsulfonyl)phenylboronic acid (5.64g, 28.2mmol), potassium phosphate (12.0g, 56.4mmol) and DMF (50mL) under an atmosphere of nitrogen was added palladium *tetrakis*triphenylphosphine (1.36g, 1.18mmol). After heating at 120°C for 14 hours, the reaction was cooled and the DMF removed *in vacuo*. The residue was partitioned between ethyl acetate (100mL) and water (100mL), separated and the organic layer dried over sodium sulfate and concentrated *in vacuo*. Purification by silica chromatography eluting with a gradient of ethyl acetate in cyclohexane gave the title compound (4.29g, 74%) TLC R_F 0.19 (1:1 ethyl acetate:cyclohexane) LC retention time 2.36mins, MS m/z 248 (MH^+)

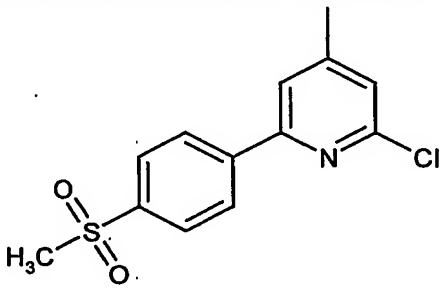
Intermediate 5
2-[4-(methylsulfonyl)phenyl]-4-methylpyridine-*N*-oxide



A solution of intermediate 4 (3g, 12.2mmol) in dichloromethane (5mL) was added to a solution of 3-chloroperbenzoic acid (7.35g of 57 to 86% grade material) in dichloromethane (15mL) at reflux. After stirring for 3 hours at this temperature, the reaction was cooled, washed sequentially with saturated aqueous sodium bicarbonate solution, saturated aqueous sodium sulfite solution and water, dried over sodium sulfate and concentrated *in vacuo* to give the title compound (3.11g, 97%) LC retention time 1.94mins, MS m/z 264 (MH^+)

Intermediate 6

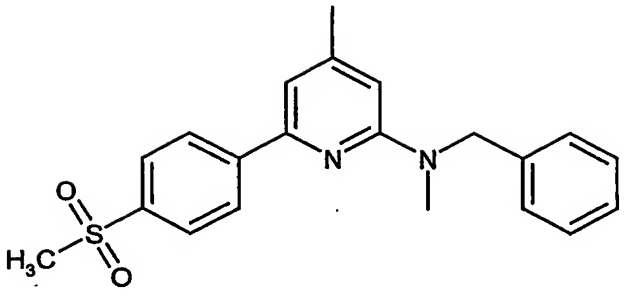
2-Chloro-4-methyl-6-[4-(methylsulfonyl)phenyl]pyridine



A mixture of intermediate 5 (3.11g, 11.8mmol) and phosphorus oxychloride (10mL) was heated at 100°C for 14 hours. After cooling, the reaction was quenched with saturated aqueous sodium bicarbonate solution, with cooling, extracted with dichloromethane and the combined organic extracts dried over sodium sulfate and concentrated *in vacuo*. Purification by silica chromatography eluting with a gradient of ethyl acetate in cyclohexane gave the title compound (1.91g, 58%) TLC R_F 0.35 (1:1 ethyl acetate:cyclohexane) LC retention time 3.13mins, MS m/z 282 (MH^+)

Example 3

N-Benzyl-N-methyl-4-methyl-6-[4-(methylsulfonyl)phenyl]pyridine-2-amine

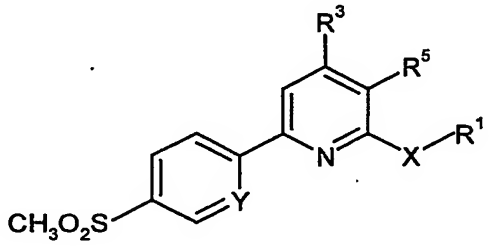


A solution of intermediate 6 (10mg, 0.04mmol) and N-methylbenzylamine (20mg, 0.18mmol) in NMP (0.5mL) was heated at 250°C in the microwave for 10minutes. Removal of the solvent (vacuum centrifuge) and purification by silica chromatography, eluting with a gradient of cyclohexane to ethyl acetate, gave the title compound (5mg) LC retention time 3.62mins, MS m/z 367 (MH^+).

Examples 4 to 67

- Examples 4 to 67, as shown in Tables 1 to 3 that follow, were prepared in the manner described for Examples 1 to 3 as appropriate.

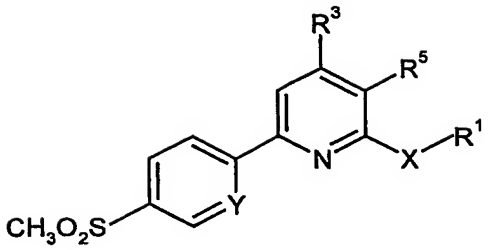
Table 1



(I)

Ex	R^1	X	R^3	R^5	Y	MS
4	4-chlorobenzyl	NH	CH_3	H	C	MH+ 387
5	benzyl	NCH_3	CF_3	H	C	MH+ 421
6	2-furylmethyl	NH	CF_3	H	C	MH+ 397
7	benzyl	NH	CH_3	H	C	MH+ 353
8	cyclohexanemethyl	NH	CF_3	H	C	MH+ 413
9	4-methoxyphenyl	NH	CH_3	H	C	MH+ 369
10	2-methylpropyl	O	CH_3	H	C	MH+ 320
11	3-pyridyl	O	CH_3	H	C	MH+ 341

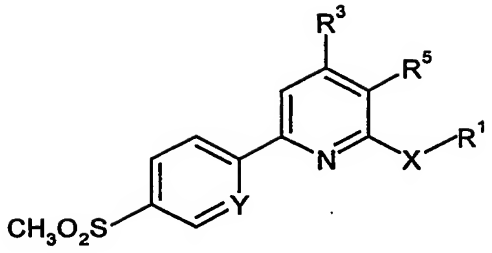
Table 1



(I)

Ex	R^1	X	R^3	R^5	Y	MS
12	allyl	NH	CF_3	H	C	MH+ 357
13	2-chlorophenyl	NH	CH_3	H	C	MH+ 373
14	3,5-difluorobenzyl	NH	CH_3	H	C	MH+ 389
15	3-pyridinemethyl	NH	CH_3	H	C	MH+ 354
16	4-methoxyphenyl	NH	CF_3	H	C	MH+ 423
17	cyclohexyl	NH	CH_3	H	C	MH+ 345
18	n-butyl	NH	CF_3	H	C	MH+ 373
19	2-methylpropyl	NH	CF_3	H	C	MH+ 373
20	4-methoxybenzyl	NH	CH_3	H	C	MH+ 383
21	4-fluorobenzyl	NH	CH_3	H	C	MH+ 371
22	2-(5-methylfuryl)methyl	NH	CF_3	H	C	MH+ 411
23	n-butyl	NH	CH_3	H	C	MH+ 319
24	2-furylmethyl	NH	CH_3	H	C	MH+ 343
25	4-methylbenzyl	NH	CH_3	H	C	MH+ 367
26	cyclopentyl	NH	CF_3	H	C	MH+ 385
27	4-pyridinemethyl	NH	CH_3	H	C	MH+ 354
28	2-pyridinemethyl	NH	CH_3	H	C	MH+ 354
29	2-(6-methylpyridine)methyl	NH	CH_3	H	C	MH+ 382
30	4-ethoxybenzyl	NH	CH_3	H	C	MH+ 397
31	2-methylpropyl	NH	CH_3	H	C	MH+ 319

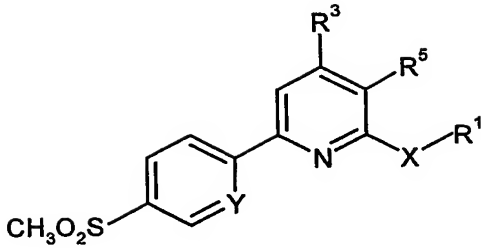
Table 1



(I)

Ex	R^1	X	R^3	R^5	Y	MS
32	propargyl	NH	CF_3	H	C	MH+ 355
33	cyclohexanemethyl	NH	CH_3	H	C	MH+ 359
34	4-pyranylmethyl	NH	CH_3	H	C	MH+ 361
35	2-tetrahydrofurylmethyl	NH	CH_3	H	C	MH+ 347
36	2,2-dimethylpropyl	NH	CH_3	H	C	MH+ 333
37	2,2,2-trifluoroethyl	NH	CH_3	H	C	MH+ 345
38	n-butyl	NCH_3	CH_3	H	C	MH+ 333
39	ethyl	NEt	CH_3	H	C	MH+ 319
40	benzyl	NH	CF_3	H	C	MH+ 407
41	4-methylphenyl	NH	CH_3	H	C	MH+ 353
42	2-furylmethyl	NH	CH_3	H	C	MH+ 343
43	4-fluorophenyl	NH	CH_3	H	C	MH+ 357
44	2-thiophenylmethyl	NH	CH_3	H	C	MH+ 359
45	benzyl	NCH_3	C_2H_5	H	C	MH+ 381
46	4-pyranylmethyl	NH	C_2H_5	H	C	MH+ 375
47	2-methylpropyl	NH	C_2H_5	H	C	MH+ 333
48	4-methylbenzyl	NH	CF_3	H	C	MH+ 421
49	2-methylbenzyl	NH	CF_3	H	C	MH+ 421
50	2-chlorobenzyl	NH	CF_3	H	C	MH+ 441
51	2-(5-methylpyrazine)methyl	NH	CF_3	H	C	MH+ 423

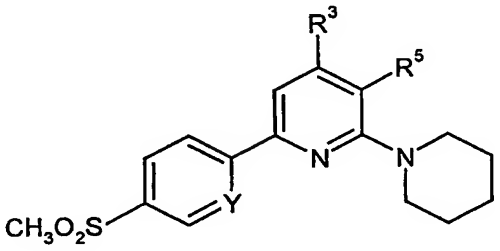
Table 1



(I)

Ex	R^1	X	R^3	R^5	Y	MS
52	(S)-α-methylbenzyl	NH	CF_3	H	C	MH+ 421
53	(R)-α-methylbenzyl	NH	CF_3	H	C	MH+ 421
54	cyclohexyl	NH	CF_3	H	C	MH+ 399
55	4-methoxybenzyl	NH	CF_3	H	C	MH+ 437
56	6-methylpyridin-3-yl	NH	CH_3	H	C	MH+ 354
57	benzyl	NH	H	CH_3	C	MH+ 353
58	benzyl	NCH_3	CH_3	CH_3	C	MH+ 381
59	benzyl	NH	CH_3	CH_3	C	MH+ 367
60	2-methylpropyl	NH	CH_3	CH_3	C	MH+ 333
61	benzyl	NCH_3	H	H	C	MH+ 353
62	benzyl	NCH_3	CH_3	H	N	MH+ 368
63	4-methoxybenzyl	NH	CH_3	H	N	MH+ 370
64	2-methoxyethyl	NH	CH_3	H	C	MH+ 321

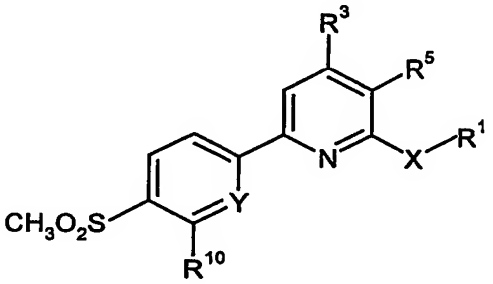
Table 2



(I)

Ex	R^3	R^5	Y	MS	
65	C_2H_5	H	C	MH+	345
66	CH_3	CH_3	C	MH+	345

Table 3



(I)

Ex	R^1	X	R^3	R^5	R^{10}	Y	MS	
67	benzyl	NH	CH_3	H	F	C	MH+	353

Biological Data

Microsomal Assay

Inhibitory activity against microsomal h-COX2 was assessed against a microsomal preparation from baculovirus infected SF9 cells. An aliquot of microsomal preparation was thawed slowly on ice and a 1/40,000 dilution prepared from it into the assay buffer (sterile water, degassed with argon containing 100mM HEPES (pH 7.4), 10mM EDTA (pH7.4), 1mM phenol, 1mM reduced glutathione, 20mg/ml gelatin and 0.001mM Hematin). Once diluted the enzyme solution was then sonicated for 5 seconds (Branson sonicator, setting 4, 1cm tip) to ensure a homogeneous suspension. 155µl enzyme solution was then added to each well of a 96-well microtitre plate containing either 5µl test compound (40x required test concentration) or 5µl DMSO for controls. Plates were then mixed and incubated at room temperature for 1 hour. Following the incubation period, 40µl of 0.5µM arachidonic acid was added to each well to give a final concentration of 0.1µM. Plates were then mixed and incubated for exactly 10 minutes (room temperature) prior to addition of 25µl 1M HCl (hydrochloric acid) to each well to stop the reaction. 25µl of 1M NaOH (sodium

hydroxide) was then added to each well to neutralise the solution prior to determination of PGE_2 levels by enzyme immunoassay (EIA).

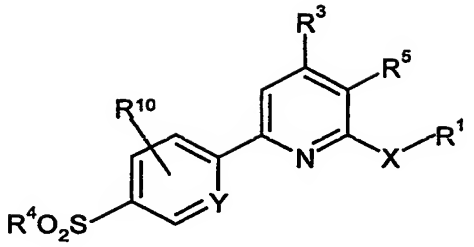
The following examples had IC_{50} values for inhibition of COX-2 of 0.5μM or less and at least a 100-fold selectivity for COX-2 over COX-1, based on comparison of the respective IC_{50} values.

1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 43, 44, 45, 46, 47,48, 49, 50, 51, 52, 53, 54, 55, 56, , 57, 58, 59, 60, 61, , 62, 63,66, 67.

The application of which this description and these claims form a part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be be directed to any novel feature or combination of features relating to the invention described herein. They may take the form of a product, process or use claims and may include, by way of example and without limitation the claims that follow.

CLAIMS

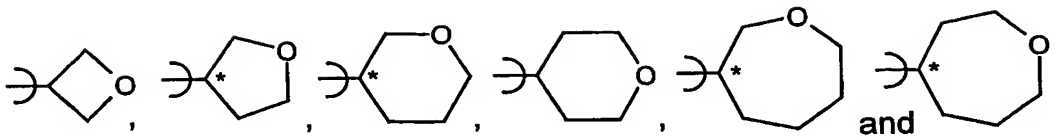
1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof in which:

X is selected from the group consisting of oxygen or NR^2;
Y is selected from the group consisting of CH or nitrogen;
R^1 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-2}alkyl substituted by one to five fluorine atoms, C_{1-3}alkylOC_{1-3}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-10}cycloalkylC_{0-6}alkyl, C_{4-12}bridged cycloalkyl, $A(CR^6R^7)_n$ and $B(CR^6R^7)_n$;
R^2 is selected from the group consisting of H and C_{1-6}alkyl; or
R^1 and R^2, together with the nitrogen atom to which they are attached form a 4-8 membered saturated heterocyclic ring such as a pyrrolidine, morpholine or piperidine ring;
R^3 is selected from the group consisting of C_{1-5}alkyl and C_{1-2}alkyl substituted by one to five fluorine atoms;
R^4 is selected from the group consisting of C_{1-6}alkyl, NH_2 and R^9CONH;
R^5 is selected from the group consisting of hydrogen, C_{1-3}alkyl, C_{1-2}alkyl substituted by one to five fluorine atoms, halogen, cyano, $(C_{1-3}alkyl)_2NCO$, C_{1-3}alkyl$S$ and C_{1-3}alkylO_2S;
R^6 and R^7 are independently selected from H or C_{1-6}alkyl;
A is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R^8;
R^8 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one more fluorine atoms, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more F, NH_2SO_2 and C_{1-6}alkylSO_2;
B is selected from the group consisting of



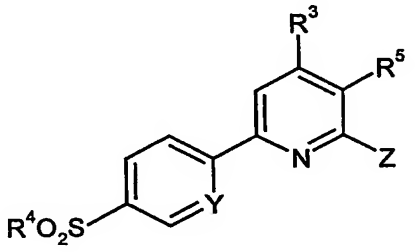
and where

) defines the point of attachment of the ring;

R^9 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylOC_{1-6}alkyl, phenyl, HO_2CC_{1-6}alkyl, C_{1-6}alkyl$OCOC_{1-6}$alkyl, C_{1-6}alkylOCO, H_2NC_{1-6}alkyl, C_{1-6}alkyl$OCONHC_{1-6}$alkyl and C_{1-6}alkyl$CONHC_{1-6}$alkyl;
R^{10} is selected from the group consisting of H and halogen; and
n is 0 to 4.

2. A compound of formula (I) as described in any of Examples 1 to 67.

3. A process for the preparation of compounds of formula (I) as defined in any of claims 1 or 2 which comprises reacting a compound R^1XH of formula (II), or a protected derivative thereof, with a compound of formula (III)



(III)

where X is as defined and Z is halogen or a sulfonate, and thereafter and if necessary, interconverting a compound of formula (I) into another compound of formula (I), and/or deprotecting a protected derivative of compound of formula (I).

4. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 or 2 in admixture with one or more physiologically acceptable carriers or excipients.

5. A compound of formula (I) as defined in any one of claims 1 or 2 for use in human or veterinary medicine.

6. A method of treating a human or animal subject suffering from a condition which is mediated by COX-2 which comprises administering to said subject an effective amount of a compound of formula (I) as defined in any one of claims 1 or 2.

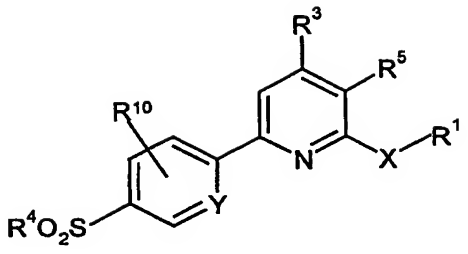
7. A method of treating a human or animal subject suffering from an inflammatory disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) as defined in any one of claims 1 or 2.

8. The use of a compound of formula (I) as defined in any one of claims 1 or 2 for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by COX-2.

9. The use of a compound of formula (I) as defined in any one of claims 1 or 2 for the manufacture of a therapeutic agent for the treatment of an inflammatory disorder.

Abstract

Compounds of formula (I)



(I)

or pharmaceutically acceptable salts thereof are potent and selective inhibitors of COX-2 and are of use in the treatment of the pain, fever and inflammation of a variety of conditions and diseases.